

### **Remarks/Arguments**

Reconsideration and allowance are respectfully requested. Claims 26-29 and 36-72 are pending and are at issue. Claims 26, 37, and 40 have been amended for a second time to clarify the patient to whom the GLP-1 agonist is administered and to conform with proper Markush format. The amendments to claims 26, 37, and 40 do not add new matter and will not require any further search by the Examiner. Accordingly, the Examiner is requested to enter these amendments.

The presently pending claims must be properly construed before the Examiner's rejections can be addressed. The present claims include three independent claims. Pertinently, each claim preamble specifies what the claimed method will accomplish, and each claim body expressly describes the patient who is the subject of the administration of GLP-1 agonist. Claim 26 specifically provides that the method is directed to intentionally lowering one or more serum lipid levels and that the patient is "a patient in need of having one or more serum lipid levels lowered." Claim 37 specifically provides that the method is directed to reducing of the LDL:HDL ratio and that the patient is "a patient in need of reduction of said LDL:HDL ratio." Claim 40 specifically provides that the method is directed to reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) and that the patient is "a patient in need of reduction of the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A))."

The preambles of these claims set forth the objectives of the claimed methods, and the bodies of these claims direct that the method be performed on someone "in need". The claims' recitations of a patient "in need" gives life and meaning to the preambles' statements of purpose. Therefore, these preambles are not merely statements of effects that may or may not be desired or appreciated. Rather, they are statements of the intentional purpose for which each method must be performed. The claims require the intent of achieving the purpose given in their respective preambles. In other words, administering the claimed GLP-1 agonists for some purpose other than intentionally lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40) is not a claimed method. The present claims are properly interpreted to mean that a GLP-1 agonist must be administered to a patient intentionally to lower one or more serum lipid levels (claim 26), to reduce of the LDL:HDL ratio (claim 37), or to reduce the serum level of lipoprotein A

(lp(A)) and/or apolipoprotein A (apo(A)) (claim 40).

This is precisely the construction that has been mandated by the Court of Appeals for the Federal Circuit. *Jansen v. Rexall* 342 F.3d 1329, 68 U.S.P.Q.2d 1154 (Fed Cir. 2003). The *Jansen* court construed a claim directed to a method of treating macrocytic-megaloblastic anemia by administering certain vitamins. The preamble of the claim at issue provided the objectives of the claimed method (i.e., treating or preventing macrocytic megaloblastic anemia), and the bodies of the claim directed that the method be performed on someone “in need”. The Federal Circuit held that this combination of preamble limitation and body limitation must be construed to require intent of treating the stated disease.

The *Jansen* Court held that there was no proof of direct infringement, and consequently no inducement of or contributory infringement, because there was no proof that anyone had taken the vitamins with the intent of treating or preventing macrocytic-megaloblastic anemia. The mere administration of these vitamins to patients who may have had this disease or in whom this disease may have been prevented was not an infringement in the absence of intent or purpose by the patients because such intent was a claim limitation expressed by the stated purpose in the claim preamble and “in need” in the claim body.

#### **REJECTION OF THE CLAIMS UNDER 35 USC 102 (b)**

Claims 26-29 and 36-42 stand rejected under 35 U.S.C. 102(b) as anticipated by Eng (US patent 5,424,286) in view of Raufman et al [*J.Biol. Chem.*, (1992) 267: 21432-21437] and Howard. The Examiner asserts that Eng discloses the treatment of diabetes mellitus in any and/or all diabetic patients and adds Howard as disclosing that therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension and/or obesity. The Examiner concludes that “[H]ence any and/or all such diabetic patients clearly encompasses diabetic patients with dyslipidemia .....[A]lternatively, the treatment of dyslipidemia, as claimed, clearly overlaps the treatment of diabetes and/or obesity.” (page 3 of present Office Action). The Examiner adds that “it is not necessary that that ‘patient in need of such treatment’ (the missing descriptive matter) necessarily be present in Eng’s treatment of diabetes mellitus (the thing described in the reference), and that it would be so recognized by persons of ordinary skill, because any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment” (page 3 of Office Action, emphasis

added)

Applicants respectfully traverse this rejection.

First, the test for anticipation is whether, “each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference” or prior public use. *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir.), *cert. denied*, 488 U.S. 892 (1988); *Minnesota Mining and Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.* 976 F.2d 1559, 1565 (Fed. Cir. 1992); *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). “When more than one reference is required to establish unpatentability of the claimed invention anticipation under §102 can not be found ....” *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991).

The Examiner has relied upon a combination of references, and for that reason, the anticipation rejection is incorrect and must be withdrawn.

Second as the Examiner admits, Eng merely discloses the treatment of diabetes mellitus in any and/or all diabetic patients. Eng did not administer any substance with the intention of lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40).

The *Jansen* appellate court relied upon its earlier decision in *Rapoport v. Dement*, 254 F.3d 1053, 59 U.S.P.Q.2d 1215 (Fed. Cir. 2001). The issue in *Rapoport* was whether a claim to a method for treating sleep apnea by administration of a therapeutically effective amount of an azapirone compound to a patient in need of such treatment was invalid over a prior art reference disclosing administration of an azapirone compound to patients with anxiety. The Patent Office argued that the latter inherently anticipated the former even though the reference only disclosed the treatment of anxiety in patients suffering from sleep apnea and did not address treatment of the underlying sleep apnea disorder. The *Rapoport* court found that while the reference mentioned the possibility of administering the compound to patients suffering from sleep apnea, it was “for the purpose of treating anxiety in such patients, not for the purpose of treating the sleep apnea disorder”. Thus, while the reference at issue in *Rapoport* disclosed administering an azapirone compound to patients suffering from sleep apnea, the Federal Circuit held that the reference did not anticipate the claim at issue because the compound was administered for the purpose of treating anxiety in this patient population.

Similarly, in the present case, Eng discloses the administration of exendin to diabetic patients but for the purpose of treating hyperglycemia and not for the purpose of lowering serum lipid levels. Therefore, Eng does not disclose the claimed methods of intentionally lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40). Eng does not anticipate the present claims.

Third, “[a]n anticipatory reference, however, need not duplicate word for word what is in the claims. Anticipation can occur when a claimed limitation is ‘inherent’ or otherwise implicit in the relevant reference.” *Standard Havens Prods., Inc. v. Gencor Indus., Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991), *cert. denied*, 506 U.S. 817 (1992). A characteristic is inherent in a reference when evidence makes it clear that the missing descriptive matter is necessarily present in the reference and that it would be so recognized by persons of ordinary skill. *Continental Can*, 948 F.2d at 1268. The Examiner has not proven that lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40), whether intentional or not, is inherently disclosed by Eng. It cannot be determined whether every time that Eng administered a GLP-agonist that the treated patient was lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40). Therefore, such effect was not an inherent property of the Eng administrations. Indeed, there is no evidence in Eng that any of his patients ever received the presently claimed treatment. Eng does not inherently anticipate the present claims.

Finally, one simple test to determine whether a reference or use is anticipatory is to determine whether that reference or use would literally infringe the claim at issue, because “[t]hat which would *literally* infringe if later in time anticipates if earlier than the date of invention.” *Lewmar Marine, Inc. v. Barient, Inc.* 827 F.2d 744, 747 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 1007 (1988). *Jansen* makes it clear that treating diabetes mellitus in a diabetic patient would not infringe any of the present claims, as the present claims require intentionally lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40). Eng simply does not disclose this, practicing Eng would not infringe these claims, and consequently, Eng does not anticipate the present claims.

Accordingly, this rejection should be withdrawn.

**REJECTION OF THE CLAIMS UNDER 35 USC 102 (b)**

Claims 26, 27, 29, 36, 37, 39, 40 and 42 stand rejected under 35 U.S.C. 102(b) as anticipated by Efendic (US patent 5,631,2246) in view of Howard.

Efendic is cited as disclosing the treatment of obese NIDDM patients with a GLP-1 agonist (i.e., GLP-1 (7-36) amide), and Howard is added as above.

Applicants respectfully traverse this rejection.

First as above with respect to Eng, the Examiner has improperly relied upon a combination of references, and for that reason, the anticipation rejection is incorrect and must be withdrawn.

Second, Efendic, like Eng above, is totally silent as to the use of a GLP-1 agonist for intentionally lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40). Efendic merely discloses the treatment of obesity in NIDDM patients and does not anticipate the present claims.

Third, the Examiner has not proven that lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40), whether intentional or not, is inherently disclosed by Efendic. It cannot be determined whether every time that Efendic administered a GLP-agonist that the treated patient was lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40). Therefore, such effect was not an inherent property of the Efendic administrations. Indeed, there is no evidence in Efendic that any of his patients ever received the presently claimed treatment. Efendic does not inherently anticipate the present claims.

Finally, it clear that treating obesity in NIDDM patients would not infringe any of the present claims, as the present claims require intentionally lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40). Efendic simply does not disclose this, practicing Efendic would not infringe these claims, and consequently, Efendic does not anticipate the present claims.

Accordingly, this rejection should be withdrawn.

**REJECTION OF THE CLAIMS UNDER 35 USC 112, FIRST PARAGRAPH**

A. Enablement

The Examiner has rejected claims 26-29 and 36-42 under 35 U.S.C. 112, first paragraph as lacking enablement: The Examiner stated that "the specification, while being enabling for a method of lowering plasma levels of triglycerides, free fatty acids, or total cholesterol, does not reasonably provide enablement for a method of lowering one or more serum lipids, of reducing the serum LDL:HDL ratio, or of reducing the serum level of lp(A) or apo(A)." (page 5 of Office Action).

Applicants respectfully traverse this rejection.

The Examiner has not provided any reasonable basis for this rejection. Juntti-Berggren, previously relied upon by the Examiner to show that no changes were observed in the levels of LDL and HDL cholesterol after administration of GLP-1, is inappropriate.

It is scientifically impossible to draw any conclusion about the effects of GLP-1 on levels of HDL and LDL from the Juntti-Berggren study because none of the patients in the Juntti-Berggren study were ever administered GLP-1 without coadministration of insulin.

The Examiner's citation to Juntti-Berggren does not establish a reasonable basis, as required by law, to question the enablement of the claimed invention. Applicants request that the Examiner provide an Examiner's declaration explaining how one skilled in the art could draw any conclusions from the Juntti-Berggren study regarding the effects of GLP-1 without insulin coadministration on HDL and LDL levels. The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention (*In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)), and "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain **why** it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

In the absence of such a declaration, this rejection should be withdrawn because a specification must be taken in compliance with the enabling requirement of the first

paragraph of 112 unless there is reason to doubt the objective truth of the statements contained therein. Juntti-Berggren does not provide such doubt as it involves coadministration of a GLP-1 agonist and insulin.

**B. Written Description And Indefiniteness**

The Examiner rejected claims 26-29 and 36-42 under 35 U.S.C. 112, first paragraph as a lacking written description. Particularly, in the previous Office Action, the Examiner cited to the disclosure in Juntti-Berggren that no changes were observed in the levels of LDL and HDL cholesterol after coadministration of GLP-1 and insulin as objective evidence that the full scope of the claims is not described.

Applicants respectfully traverse this rejection.

In reply, Applicants noted that the present application clearly describes the use of GLP-1 agonists to lower or reduce the serum LDL:HDL ratio and the serum level of lp(A) or apo(A) (see, for example, page 5, lines 7-10 and 25-28 and page 6, lines 3-8 of the application) and that the coadministration of GLP-1 and insulin described in Juntti-Berggren teaches nothing about the effect of GLP-1 on the serum LDL:HDL ratio, or on the serum level of lp(A) or apo(A). Applicants repeat the arguments above with respect to Juntti-Berggren and submit that Juntti-Berggren does not provide any evidence to doubt the objective truth of the disclosure contained in the present application.

Again, applicants request that the Examiner provide an Examiner's declaration explaining how one skilled in the art could draw any conclusions from Juntti-Berggren regarding the effects of GLP-1 without insulin coadministration on HDL and LDL levels.

In the absence of such a declaration, this rejection should be withdrawn because a specification must be taken in compliance with the enabling requirement of the first paragraph of 112 unless there is reason to doubt the objective truth of the statements contained therein. Juntti-Berggren does not provide such doubt as it involves coadministration of a GLP-1 agonist and insulin.

The Examiner has also rejected claims 26, 27, 29, 36, 37, 39, 40, and under 35 U.S.C. 112, first paragraph as lacking a written description and claims 44-49, 52, 54-59, 62, 64-69, and 72 have been rejected under 35 U.S.C. 112, second paragraph for indefiniteness because of the terms "analogue" and "derivative". Claims 45, 49, 55, 59, 65, and 69 also stand rejected under 35 U.S.C. 112, second paragraph for indefiniteness because of the single

amino acid substitutions.

Applicants respectfully traverse these rejections.

The Examiner's attention is respectfully directed to the present detailed description of analogues, derivatives, and substitutions in the present specification at page 12, line 15-page 40, line 15. This detailed description meets the written description and definiteness requirements. Furthermore, the Examiner's attention is directed to Eng and Efendic which demonstrate that these are accepted terms in the art. The metes and bounds of these claims would be understood by those skilled in the art.

Accordingly, these rejections should be withdrawn.

#### **OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS**

The Examiner rejected claims 26-29 and 36-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 39 and 40 of U.S. Patent No. 6,268,343 in view of Howard and Efendic or claims 19 and 20 of U.S. Patent No. 6,458,924 in view of Howard and Efendic.

The Examiner asserted that "although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is directed to or encompasses the administration of Arg<sup>34</sup>, Lys<sup>26</sup>(N-ε-(γ-Glu(N-α-hexadecanoyl))) -GLP-1(7-37) for the treatment of diabetes and obesity. Essentially any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment because such treatment lowers the risk of cardiovascular disease in accordance with the present specification at page 2, full paragraph 2." (pages 10 and 11 of Office Action).

Applicants respectfully traverse this rejection.

These obviousness-type double patenting rejections are based on the assertion that the present methods of lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40) are obvious over the cited claims of U.S. Patent Nos. 6,268,343 and 6,458,924 because "essentially any and/or all patients, including diabetic and/or obese patients", are patients in need of having their serum lipids lowered. However, neither of these patents claim administering any substance with the intention of lowering one or more serum lipid levels (claim 26), reducing of the LDL:HDL ratio (claim 37), or reducing



Application Serial No.: 09/800,541  
Inventors: Knudsen et al.  
Express Mail Label No.: EV 409530823 US

the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)) (claim 40), and there is motivation in these patents to do so with any reasonable expectation of success. The Examiner is applying the improper "obvious to try" standard to reach his conclusion of obviousness-type double patenting. Efendic is also distinguished as above.

Accordingly, applicants respectfully request withdrawal of these obviousness-type double patenting rejections.

In view of the above amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this response or application.

Respectfully submitted,



Date: June 1, 2004

Rosemarie R. Wilk-Orescan,  
Reg. No. 45,220 for:  
Richard W. Bork, Reg. No. 36,459  
Novo Nordisk Pharmaceuticals, Inc.  
100 College Road West  
Princeton, NJ -8540  
(609) 987-5800

Customer Number 23650  
PATENT TRADEMARK OFFICE